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1350 '99 MAR 30 March 31, 1999

Dockets Management Branch(HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket No. 98D-0994; Draft Guidance for Industry on
BACPAC I: Intermediates in Drug Substance Synthesis;
Bulk Actives Post-approval Changes: Chemistry,
Manufacturing and Controls (CMC) Documentation; Notice
of Availability Appearing in the Federal Register of
November 30, 1998 (63FR65793)

Dear Sir/Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, happier and more productive lives. Investing nearly \$24 billion a year in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures.

PhRMA member firms are either sponsors of new drug applications (NDAs) and abbreviated new drug applications (ANDAs), or holders of drug master files that are referenced in such applications, and are required from time to time to make certain post-approval changes in those applications. Our members are, therefore, vitally interested in this subject draft guidance which would define recommended chemistry, manufacturing and control tests, and documentation necessary to support such changes.

PhRMA has a long history in advocating efforts to improve and streamline the FDA's administrative review and approval process for post-approval manufacturing or technical changes to approved new drug applications. Since the early 1980s, these efforts have included:

- (1) Comments on and active support of the FDA proposed rewrite of the New Drug and Antibiotic Regulations (47FR46622, October 19, 1982) that resulted in some meaningful changes to the regulations governing CMC changes that were finalized in 1985;

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- (2) Collaboration with FDA and support for the Prescription Drug User Fee Act of 1992 (PDUFA) that set statutory milestones for the performance of reviews of manufacturing supplements for approved NDAs;
- (3) Support for the Clinton Administration National Performance Review (Reinventing Drug & Medical Device Regulations, April, 1995) (REGO) recommendations that FDA significantly reduce the number of manufacturing changes that require prior FDA approval; and more recently,
- (4) Further collaboration with FDA and support for statutory provisions relating to improved management of the manufacturing supplement review and approval process, including enhanced PDUFA management milestones for manufacturing supplements in the Food and Drug Administration Modernization Act of 1997 (FDAMA).

More specifically relating to the subject draft guidance, PhRMA actively supported FDA Center for Drug Evaluation and Research efforts to develop new industry guidance applicable to the documentation necessary to support manufacturing and other technical changes to approved drug applications and drug master files for drug substances or active pharmaceutical ingredients. Those efforts included:

- (1) Participation in the planning and conduct of the FDA/AAPS sponsored "Bulk Active Post-Approval Changes" Workshop held during March 25-27, 1997;
- (2) Publication of PhRMA Decision Tree for Bulk Active Post-Approval Changes in Pharmaceutical Technology in September, 1998 (copy attached); and
- (3) Submission of PhRMA recommendations to FDA on implementing the FDAMA provisions relating to Manufacturing Changes, including the PhRMA BACPAC Decision Tree.

All of the above efforts on behalf of the research-based industry were intended to bring about substantive changes to the process that FDA uses to review and approve manufacturing or technical changes to already approved drug applications so that the resource and regulatory burdens on both the FDA and the industry are commensurate with principles of sound science, advances in technology and adequate protection of the public health. With the impetus of PDUFA, REGO and now FDAMA, PhRMA believes that the FDA has both the legislative authority and the flexibility to effect meaningful changes in the manufacturing change supplement process and our comments on the subject BACPAC I draft guidance are intended to assist in that endeavor.

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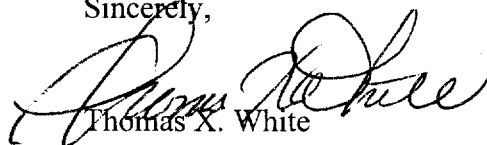
PhRMA views the draft BACPAC I as providing substantial regulatory relief with regard to changes up to and including the final intermediate step. The draft guidance contains sufficient detail that regulatory decisions are now much clearer for post-approval changes made in early synthetic steps. The general approach of comparing the equivalence of material pre- and post-change represents a rational, scientific method for evaluation of the impact of a given change. The filing requirements in the draft guidance reflect the results of this evaluation and provide considerable regulatory relief from those currently delineated in 21 *CFR* 314.70. Significant benefit to industry is also realized with the ability to demonstrate equivalence based on the impurity profile of synthetic intermediates after the change, without always requiring evaluation of the Active Pharmaceutical Ingredient (e.g. physical properties or stability).

It is acknowledged by PhRMA member firms that for many older processes, analytical methodology is not currently in place for full characterization of the impurity profiles of synthetic intermediates. In such cases, the development and validation of adequate analytical methods for quantifying existing and new impurities may be considered too costly to take advantage of the regulatory relief offered by evaluation of changes at the process intermediate stage. For recent and future filings, more detailed in-process specifications and test methods are available and evaluation of changes will be effectively carried out early in the synthesis with these tools.

Based upon an extensive review of the draft guidance by PhRMA's technical committees, the attached general and specific comments are provided with a view to improve the understanding and clarity of the document as to its applicability and scope for documentation requirements for changes made up to and including the "final" intermediate. PhRMA understands that FDA currently has under development an additional draft guidance which would cover those manufacturing changes beyond the final intermediate, including the final drug substance or active ingredient.

On behalf of our members, we appreciate very much the opportunity to provide comments on this important draft guidance for industry. PhRMA and its technical committees offer continuing assistance in further Agency efforts to develop appropriate guidance applicable to drug substance manufacturing changes.

Sincerely,



Thomas X. White

Attachments: General and Specific Comments; PhRMA BACPAC Decision Tree Article

Attachment

PhRMA General and Specific Comments on FDA Draft Guidance for Industry:

BACPAC I: Intermediates in Drug Substance Synthesis.

Docket No. 98D-0994

March 31, 1999

General Comments:

The following discussion briefly summarizes the key issues from PhRMA's review of this draft guidance. A detailed list of comments (with reference to specific line numbers) is also provided.

We understand the changes covered by BACPAC I to be within the stated intent of 21 *CFR* 314.70(a), which would encompass changes in the information filed in the approved application. For example, details regarding equipment used in early steps and scale of manufacture are not always included in regulatory filings. It is recommended that the section on scale changes be dropped, since the majority of scale changes are driven by changes in equipment or site, which are handled in other sections of the guidance.

One area of concern is the level of documentation requested in support of changes. In some areas, the required data and information are greater than that provided in an NDA filing. It is the experience of PhRMA companies that analytical methods for raw materials and intermediates are briefly summarized and no accompanying validation data are provided in original NDA filings. The in-process methods are validated for their intended use and the detailed validation data would be available for inspection. The requirement of certificates of analysis for raw materials and starting materials is another example of additional detail not typically provided. A batch data summary for the relevant materials should meet the requirement. In the case of the redefinition of an intermediate as a starting material, the list of sources and the change-control protocol are considered GMP considerations that should not be included in a filing, but rather should be available for an inspection.

The extent of the comparison to demonstrate equivalence of pre-change (10 batches) and post-change (3 batches) material has been clearly indicated. It is suggested that the number of pre-change batches be indicated as "ten or more, if possible". For certain low volume or recently approved drug substances, the historical database may not include ten commercial scale batches. In such cases, the firm should be allowed to provide justification for the use of less than ten historical batches or be permitted to use pilot scale, development and clinical batches. If the use of statistical limits is not feasible, a direct comparison of data should be permissible. Where limits have been established for

specific impurities in an intermediate, meeting these limits would demonstrate equivalence for those impurities.

When the assessment extends to the drug substance, the need for physical property evaluation should not include cases where impurity profile equivalence is demonstrated at the crude drug substance prior to a step involving complete dissolution of the material.

Given that this guidance only deals with changes up to the final intermediate, some changes in the indicated type of filings are suggested. An Annual Report is suggested for site changes to a site that is currently manufacturing/testing a FDA-approved product/intermediate, which uses a similar process or technology, and that has a current satisfactory GMP inspection by FDA or a governmental authority recognized by FDA. If the only change made is a change in specifications driven by an analytical method change to an equivalent or better method, filing in an Annual Report is considered appropriate. Similarly if a change in specifications of the final intermediate is driven solely by an analytical method change, this specification change should fall under BACPAC I.

For manufacturing process changes where equivalence is demonstrated prior to the final intermediate, the relative risk of such a change is very low given the subsequent processing. Therefore, process changes for which equivalency is shown before or at the final intermediate are suggested as Annual Report filings. Where equivalence was not shown until the final drug substance, a Changes Being Effectuated supplement could be the filing mechanism. Similarly, the choice of filing mechanism for synthetic route changes up to the stage of the final intermediate could also be based on the point at which equivalence is demonstrated.

Specific Comments

The following represent specific comments on specific text (designated by line) of the draft guidance document. Comments have been grouped as major, minor or clarification through changes in wording. When a comment applies to a section that is repeated several times in the document (i.e. Test Documentation), the comment is shown with the first line of text that it refers to and subsequent lines of the same text are referenced. Text that is suggested for addition is generally underlined to differentiate it from existing wording.

I. Introduction

Major Comment

Line 16 It is recommended that the specifications for the final intermediate be included, particularly since analytical method changes that could drive a change in final intermediate specifications are included. This would be analogous with inclusion of drug substance specifications in BACPAC II.

II. General Considerations

Major Comment

Line 120-121

Replace the sentence: "When new methods are developed for this purpose, validation data should be provided" with New methods that are developed should be appropriately validated for the intended purpose and the validation data should be available for inspection.

A. Equivalence of Impurity Profiles

Minor Comments

Line 124 Modify "ten or more premodification (may include pilot scale, development and clinical) ~~commercial~~ batches

Line 128 Modify "~~at least~~ three"

Line 129 It is suggested that the demonstration of equivalence may take place at an *in situ* intermediate, if appropriate justification is provided, and that the line should read isolated (*in situ*, if appropriately justified). (also applies to line 159)

Line 132 To comply with ICH (which applies to final drug substance), delete "at or" since unspecified impurities above 0.1% are the issue.

Line 137 Modify to include any specifications for specific impurities that have been filed for an intermediate:
Existing impurities, including residual organic solvents, if relevant, are within the stated limits or, if not specified, at or below the upper statistical limits of historical data.

Line 139 Modify to include specification for total impurities that has been filed for an intermediate:
Total impurities are within the stated limits or, if not specified, at or below the upper statistical limit of historical data.

B. Equivalence of Physical Properties

Major Comments

Line 191 If impurity profile equivalence is demonstrated at the crude drug substance stage then physical property evaluation should not be required. Suggest change from “prior to or at the final intermediate” to “prior to the final API”.

Line 200 Add the underlined text:
Conformance to historical particle size distribution profile, when acceptance criteria do not exist.

A. Site, Scale, and Equipment Changes

1. Site Changes

Major Comments

Line 234 Include information regarding the current status of site for manufacturing/testing a FDA-approved product/intermediate which uses a similar process or technology, and if the site has a current satisfactory GMP inspection by FDA or a governmental authority recognized by FDA.

Line 241 Indicate brief description of analytical methods, since for intermediate testing only a short summary of type of method and conditions is typically provided in the NDA. (also applies to lines 287, 346, 372, 415, 454 and 508)

Lines 243-245

For in-process tests or tests on intermediates, validation data are not routinely included in the NDA filing. It is suggested that the sentence “Validation data should be provided for new test methods and also for existing methods if their use is being extended beyond their original purpose” be replaced with These methods should be appropriately validated. This evaluation will not necessarily result in additional specifications or testing requirements. (also applies to lines 289, 333, 348, 375, 417, 456 and 511)

Lines 259-260 The requirement for a certificate of analysis for each outsourced intermediate could also be addressed by a compilation of batch data. (also applies to lines 259, 305, 391, 439, 477 and 534)

Minor Comment

Lines 262-272

It is suggested that an Annual Report be the filing for a change to a site that meets the following criteria:

- currently manufacturing/testing a FDA-approved product/intermediate, which uses a similar process or technology
- current satisfactory GMP inspection by FDA or a governmental authority recognized by FDA.

2. Scale Changes

Major Comments

It is recommended that scale changes not be included as a separate category, since other changes handled elsewhere in this guidance (i.e. equipment or site) typically accompany scale changes. Since no attempt is made to classify scale changes (lines 275, 276) this section could be interpreted that all changes, no matter how minor, need to be reported in the annual report. Inclusion of a minimum factor (e.g. 10x) below which changes need not be reported is suggested.

A. Specification Changes

Major Comments

Line 328 As discussed in the introduction, changes to final intermediate specifications should be included under BACPAC I.

Lines 349-350 and line 391

Inclusion of COA's for raw materials and solvents is not considered necessary based on the early stage of the synthetic process. Batch data for intermediates should appropriately address this item.

Line 354 and line 395

If the only change made is a specification change, then reporting by Annual Report is considered appropriate. Also for deleting a test or replacing an analytical method, supporting impurity profile documentation may not be appropriate. If another type of change were also made (i.e. manufacturing process) that led to the specification change, then evaluation of equivalence would need to be demonstrated and the designated filing mechanism used.

Minor Comments

Line 370 Delete physical properties testing for assessment of intermediates.

B. Manufacturing Process Changes

Major Comments

Line 442 For manufacturing process changes made prior to the isolated final intermediate, reporting by an Annual Report is suggested for all cases where impurity profile equivalence is demonstrated before or at the final intermediate. For those changes in which the evaluation is carried out on the drug substance, a Changes Being Effectuated supplement is the suggested filing.

Line 480 Likewise, for changes in the route of synthesis made prior to the isolated final intermediate, reporting by an Annual Report is suggested for all cases where impurity profile equivalence is demonstrated before or at the final intermediate. For those changes in which the evaluation is carried out on the drug substance, a Changes Being Effectuated supplement is the suggested filing.

Lines 501-502 "A list of sources of the redefined starting material" is considered a GMP item that should be available for inspection, but not be included in a filing to the agency.

Lines 503-505 The change-control protocol is another GMP requirement that should be available during an inspection, but should not be required to be filed with the agency.

Minor Comments

Line 424-5 ICH Q3C states that the solvent level in the drug substance may exceed the limit in Option 1 provided that the drug product solvent level meets the criteria of Option 2. Suggested revision: The level of the new solvent in the drug substance should assure that the drug substance conforms to ICH Q3C. (also applies to lines 461-466 and 517-522)

Line 427 Delete "Option 1". (also applies to lines 461-466 and 517-522)

Clarification

Lines 32-39 Citing the text in 21 CFR 314.70(a) which states:

The applicant shall notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application.
may provide useful clarification of this paragraph.

Line 89-91 Rephrase as:

For such drug products ~~in which stability problems may potentially occur~~, the first commercial *batch* of drug product made with postchange drug substance may be included in the firm's stability testing program.

Line 95-96 This issue involves how a drug substance is defined. For example, the drug substance may be defined as a 1:1 racemic mixture or be a single enantiomer/diastereomer which contains the other enantiomer/diastereomers as low level impurities. In the case of low level isomeric impurities, the change could result in a decrease in the level of the undesired isomer and the resulting material could still be considered equivalent or better.

Suggested revision: demonstrate equivalence (e.g. chirality). ~~For example, if the drug substance is a mixture of isomers, then the same quantitative mixture should be obtained after the change.~~

Line 103 Substitute may for "should". (also applies to lines 257, 303, 389, 437, 475 and 532)

Line 115-116

Suggested revision: ~~When it is not feasible to evaluate impurities in intermediates or equivalence cannot be~~ If equivalence is not demonstrated at these stages,

Line 131 After "1. An intermediate:" add The applicant may evaluate any subsequent intermediate or the final API to confirm if impurity levels comply with this guideline.

Line 227 Change "single facility" to contiguous campus.

Line 311 Modify to "when equipment (as specified in the filing) changes alone are made".

Line 319 Change "previously used" to "previously filed".

Line 323 Add the phrase "significant change of equipment from that previously filed."

Line 325 Delete the final phrase "and documented as described for scale changes" since we have suggested deletion of that section.

Line 413 and 452 Delete physical properties testing for assessment of intermediates.

Lines 420-421 If equivalence of the impurity profile is established prior to the drug substance (even at the stage of crude API) then no physical properties testing of the drug substance should be necessary. (see comment on line 191)

Attachment B – Glossary of Terms

Line 571 Replace “processed” with produced.

Line 576 Add “Drug Substance (API)”.

Line 582 Add “covalent bond formation and/or cleavage”.

Line 585 Clarify “The step that includes solution”.

Line 589 Revise to “impurities or physical attributes (for API) from 10 or more recent batches, representative of the established process, of the intermediate or API at the point where the firm is attempting to establish equivalence”.

Line 591 Revise to “~~(The appropriate review division(s) should be contacted for concurrence~~ Written justification should be provided in those ~~rare~~ instances”.

Lines 607-608

Delete the sentence “The isolation or purification procedure should be part of the validated process.” This sentence is not relevant to the definition.

Line 633 Replace “drug substance” with material, since in BACPAC I many evaluations cover intermediates.

Lines 640-643

Align term and its definition with ICH Q7 (in working group) as follows:

API Starting Material: A material used in the production of an API which is itself or is incorporated as a significant structural fragment into the structure of the API. A starting material may be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or it may be produced in-house. Starting materials are normally of defined chemical properties and structure.

It is recommended that definitions for contiguous impurities and total impurities (as per ICH) also be included.